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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,391	02/20/2004	Pedro Aza-Blanc	P1111US10	6423

29490 7590 01/22/2007

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,391	AZA-BLANC ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9-12 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *2-5 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-12 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 1 is amended, Claims 2-5 and 9 are withdrawn, Claims 7, 8, 13-20 are cancelled and new Claims 21-26 added in the response of 11/15/06.

2. Applicants have not identified where support for amended Claim 1 and any new Claims 21-26 can be found in the originally filed specification.

Claim 1 recites "assaying kinase activity of JNK inhibitory kinase (JIK)", which finds support, inter alia, at [0038 and 0040] of the specification;

Claim 1 recites testing "modulatory agents in the presence or absence of TRAIL", which finds support, inter alia, at [0070] of the specification;.

Claim 21 recites "said JIK fragment retains kinase activity", which finds support support, inter alia, at [0038 and 0040] of the specification;

Claim 22 recites testing compounds in step (b) for the ability to "enhance TRAIL-induced apoptosis", which finds support, inter alia, at [0068] of the specification;

Claim 23 recites step (c) for contacting the modulating agents with a cell and measuring apoptosis, which finds support, inter alia, at [0069-0070] of the specification;

Claim 24 recites observing enhancing TRAIL-induced apoptosis of the cell in step (c), which finds support, inter alia, at [0070] of the specification;

Claim 25 recites that the cell is a tumor cell, which finds support, inter alia, at [0070] of the specification. Support for testing a cell in a subject finds support, inter alia, at [0010] in the specification;

Claim 26 recites a step (c), where the agent of step (b) is administered to a subject having cancer, which finds support, inter alia, at [0076-0078].

3. Claims 1-5, 9-12 and 21-26 are all the pending claims for this application.

4. Claims 1, 10-12 and 21-26 are all the pending claims under examination for this application.

5. Applicants amendments to the claims have necessitated new grounds for rejection. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawal of Objections

Claims

6. The objection to Claims 6 and 7 for reciting non-elected subject matter for polypeptide modulators is withdrawn in view of the cancelled claims.

7. The objection to Claims 6 and 7 for reciting duplicate subject as being drawn to the JIK polypeptide modulator is withdrawn in view of the cancelled claims.

Withdrawal of Rejections

35 USC § 112- second paragraph

8. The rejection of Claim 1 for the recitation "TRAIL" is withdrawn in view of Applicants amending the claim to insert "TNF-related apoptosis-inducing ligand".

9. The rejection of Claim 1 for the recitation "a biological activity of a polypeptide modulator" is withdrawn in view of the amendment of the claim to recite "kinase activity of JNK inhibitory kinase (JIK)".

10. The rejection of Claim 7 for the recitation "JIK" is withdrawn and rendered moot in view of the cancelled claim.

11. The rejection of Claim for the recitation "assaying of the biological activity of the polypeptide modulator occurs in a cell is withdrawn and rendered moot in view of the cancelled claim.

35 U.S.C. 112, first paragraph

12. The rejection of Claims 6-8 and 13 under 35 U.S.C. 112, first paragraph, for lack of enablement, is withdrawn and rendered moot in view of the cancelled claims.

35 USC § 102

13. The rejection of Claims 1 and 6-8 under 35 U.S.C. 102(b) as being anticipated by Tassi et al. (J Biol Chem 274: 33287-95, 1999) as applied to step a) of the method claims is withdrawn. Applicant's arguments, see p. 8, ¶4- p. 9, ¶9, filed in the Response of 11/15/06, have been fully considered and are persuasive. Applicants allege "The law is clear that the reference must teach each and every element of the claim to anticipate a claim. MPEP 2131", "Tassi does not teach method step b)" and "It is noteworthy that the Examiner was not able to identify any references describing an inherent or implied relationship between JIK and TRAIL-induced apoptosis."

The Examiner submits that the claim examination was based on each of steps a) and b) being separately enabled but not enabled in combination. However, Tassi does not teach each and every element of the claims.

Further, because the Examiner did not find art showing an inherent or implied relationship between JIK and TRAIL-induced apoptosis, does not rule out the possibility that one skilled in the art would simply not have combined these assay steps because they were not enabled to do so.

14. The rejection of Claims 1 and 6-8 under 35 U.S.C. 102(a) as being anticipated by De Souza et al. (Blood 99:3432-3438 (May 1, 2002) as applied to step a) of the method claims is withdrawn.

Applicant's arguments, see p. 8, ¶4- p. 9, ¶9, filed in the Response of 11/15/06, have been fully considered and are persuasive. Applicants allege "The law is clear that the reference must teach each and every element of the claim to anticipate a claim. MPEP 2131" and "De Souza does not teach method step b)."

The Examiner submits that the claim examination was based on each of steps a) and b) being separately enabled but not enabled in combination. However, De Souza does not teach each and every element of the claims.

15. The rejection of Claim 1 under 35 U.S.C. 102(b) as being anticipated by Weldon et al. (Surgery 132:293-301 (August 2002) as applied to method step b) is withdrawn.

Applicant's arguments, see p. 8, ¶4- p. 9, ¶9, filed in the Response of 11/15/06, have been fully considered and are persuasive. Applicants allege "The law is clear that the reference must teach each and every element of the claim to anticipate a claim.

MPEP 2131" and "Weldon teaches that the ability of phorbol ester (PMA) to partially suppress TRAIL-induced cell death was inhibited by BMK1/DN."

The Examiner submits that the claim examination was based on each of steps a) and b) being separately enabled but not enabled in combination. However, Weldon does not teach each and every element of the claims.

16. The rejection of Claims 1 and 12 35 U.S.C. 102(a) as being anticipated by Cantarella et al. (Cell Death and Differentiation 10:134-141 (January 2003) as applied to method step b) is withdrawn.

Applicant's arguments, see p. 8, ¶4- p. 9, ¶9, filed in the Response of 11/15/06, have been fully considered and are persuasive. Applicants allege "The law is clear that the reference must teach each and every element of the claim to anticipate a claim. MPEP 2131" and "Cantarella teaches that TIG-KIL contributes to amyloid-induced neurotoxicity in human SH-SY5Y neuronal cell line."

The Examiner submits that the claim examination was based on each of steps a) and b) being separately enabled but not enabled in combination. However, Cantarella does not teach each and every element of the claims.

Rejections Maintained

35 USC § 112- second paragraph

17. The rejection of Claim 1 for the recitation "fragment" is maintained for reasons of record. Applicant's arguments filed on p.6, ¶3 of the Response of 11/15/06 have been fully considered but they are not persuasive. Applicants allege "The amino acid sequence encoding JIK is well-characterized; thus, a "JIK fragment" is clear and definite."

The specification teaches the genus of "fragments used in the assays usually retain one or more of the biological activities of the apoptosis-modulatory polypeptide (e.g.; kinase activity if the apoptosis-modulatory employed in the first assaying step is a kinase)" [0040]. But because the specification does not specifically teach which fragment of JIK is required for kinase activity, Applicants are invited to identify and provide copies of any prior art references teaching a JIK fragment meeting all of the limitations of the claims. New Claim 21 is drawn to a JIK fragment which retains kinase activity.

18. The rejection of Claim 1 for the recitation "modulate TRAIL-induced apoptosis" is maintained for reasons of record. Applicant's arguments filed on p. 6, ¶4 have been fully considered but they are not persuasive. Applicants allege "As amended, claim 1 defines that an agent identified in step (a) to modulate JIK kinase activity is further tested in the presence or absence of TRAIL for its ability to modulate TRAIL-induced apoptosis."

Applicants' comments are not sufficient in defining what kind of assay is contemplated in step (b). Applicants' comments suggest that the assay of step (b) is an in vitro, substrate-based assay where TRAIL can be added to or deleted from the conditions. The specification teaches that TRAIL levels are endogenous to any cell [0067]. Thus one could not readily add or subtract TRAIL from a cell-based assay. But because Applicants arguments and limitations from the specification are not read into the claims, the rejection is maintained. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

35 USC § 112- first paragraph

19. The rejection of Claims 1, 10 and 11(and 12) under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained for reasons of record. Claim 12 has been added to the rejection in view of Applicants admission of record. Claim 12 is drawn to step (b) where the assay measures caspase activity modulation.

Applicant's arguments filed on p. 7, ¶1- p. 8, ¶1 have been fully considered but they are not persuasive.

a) Applicants allege "As described in Example 5 and Figure 2C, transfection of siRNAs against JIK resulted in a significant increase in TRAIL-dependent caspase activation; thus identifying JIK as a gene that inhibits TRAIL- dependent death. The increase in TRAIL-independent caspase activation is distinctly less than the significant increase in TRAIL-dependent caspase activation" (p. 7, ¶4 of the Response of 11/15/06.

The Examiner submits that despite Applicant's alleged assurances about the differences between TRAIL-independent and TRAIL-dependent caspase activation, the specification teaches "Some of the apoptosis-modulatory polypeptides (e.g., MIRSA and JIK) also modulate TRAIL-independent apoptosis, as detailed in the Examples" [0071]. And in Example 5 of the specification, Applicants specifically teach "Additionally, we noticed that these siRNAs also induced an increase in TRAIL-independent caspase activation, supporting a more general anti-apoptotic role for these genes" [0104]. Thus on the basis of Applicants own disclosure and Applicants' arguments of record, one skilled in the art would have every reason to question whether the assay of step (b) of Claim 1, using caspase activation as an endpoint or readout for TRAIL-induced apoptosis, was specific, reliable and correlative to JIK kinase activity. Absent evidence to the contrary or identification of enabling disclosure for

b) Applicants allege "the disclosure in Zhang, Herr I and Herr II is not relevant to the claimed invention."

In the Office Action of 8/17/06, the Examiner cited the three references in support of the position that Applicants specification and the field of art do not draw a clear connection between the role of JIK and TRAIL in affecting apoptosis, and what if any correlative interpretation can be made in performing methods steps a) and b) to identify a test agent for the claimed intended use. Because Applicants own specification states that both TRAIL-dependent and TRAIL-independent induced apoptosis can be mediated through JIK kinase, the references are further relevant to the original argument that the combination of JIK and TRAIL are not necessarily correlative markers for apoptosis in

just any kind of cell or cell line. The combined art disclosure of Zhang, Herr I and Herr II is dispositive to there being a strong correlation for JIK activity and TRAIL-induced apoptosis as is required for the claimed method.

c) Applicants did not address the Examiner's rejection regarding the lack of specificity and the requirement for controls using siRNA technology as specifically taught in the specification and the Aza-Blanc et al. (p. 631, Col. 1, ¶3) reference. For these reasons alone, Applicants response is incomplete.

For all of these reasons, the enablement rejection is maintained.

Grounds for New Rejections

35 U.S.C. 112, second paragraph

20. Claims 1, 10, 11 and 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1, 10, 11 and 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are in Claim 1 because it is not clear in what environment or under what conditions the interaction of the modulating agents with the TRAIL protein are tested in step (b). What aspect of TRAIL-induced apoptosis is measured? Is this a substrate-based assay or a direct measurement on a cell, which is monitored for signs of apoptosis? What are the signs for TRAIL induced apoptosis?

Further, the specification teaches "Typically, to examine apoptotic activity of a cell, the apoptosis-modulatory polypeptide is endogenously expressed in the cell" [0067]. Claims 23-25 are drawn to method step (c) where testing of modulators of TRAIL-induced apoptosis occurs in cells, but it is not clear how the limitation of step (b) (i.e., testing modulating agents in the presence or absence of TRAIL) can be met if step (b) is a cell-based assay. It seems that step (b) can only be a substrate -based assay such as caspase activity when examined in view of dependent claims 23-25.

b) Claims 10 and 11 recite the limitation "the polypeptide modulator". There is insufficient antecedent basis for this limitation in claim 1, which has been amended to JIK or JIK fragment.

c) It is not clear how Claims 10 and 11 further limit step (a) of Claim 1. Claims 10 and 11 are drawn to measuring binding and modulating the cellular level, respectively, between test agents and the polypeptide modulator. As the polypeptide modulator has been amended to JIK and its fragment, and more specifically, to measuring kinase activity, how does a binding assay or an assay for detecting changes in cellular levels correspond to the actual kinase activity itself?

e) It is not clear how Claim 26 is further limiting to Claim 1. Claim 26 is drawn to treating a patient with a TRAIL-inducing apoptosis modulatory agent, and generic Claim 1 describes a method for characterizing or identifying these agents. The further step (c) of treating a cancer subject with the method-selected agent does not contribute to or further define the method steps required in identifying an agent.

35 U.S.C. 112, first paragraph: Scope of Enablement

21. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for performing the method steps a) and b) alone for identifying JIK kinase modulatory test agents and TRAIL-induced apopstosis modulatory agents, respectively, does not reasonably provide enablement for taking a test agent that has been selected through combined methods steps a) and b) and further administering the agent to a cancer subject in order to treat the subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 26, which depends from Claim 1, is drawn to administering a TRAIL-induced apoptosis modulatory agent to a subject having any kind of cancer in order to treat the cancer.

The only modulatory agent identified by the specification is a siRNA molecule for JIK identified in HeLa cells, which blocks transcription or translational production of the protein. The siRNA could not be used in a kinase activity assay of a JIK protein, and applicants' specification does not teach any examples of other agents meeting all the requirements of steps a) and b) of Claim 1. Further, and for reasons of record, Applicants have not established that performing the claimed combined method steps would yield a modulatory agent necessarily having an effect on TRAIL-induced apoptosis, because as discussed supra, the claimed method system does not discriminate against TRAIL-independent induced apoptosis. Still further, the

specification does not provide any working examples showing that a method-selected modulatory agent would have any therapeutic effect in any cancer model much less in vivo.

Therefore, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to practicing the method steps of a) and b) much less introducing a further method step c) of treating a cancer subject encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

22. No claims are allowed.

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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